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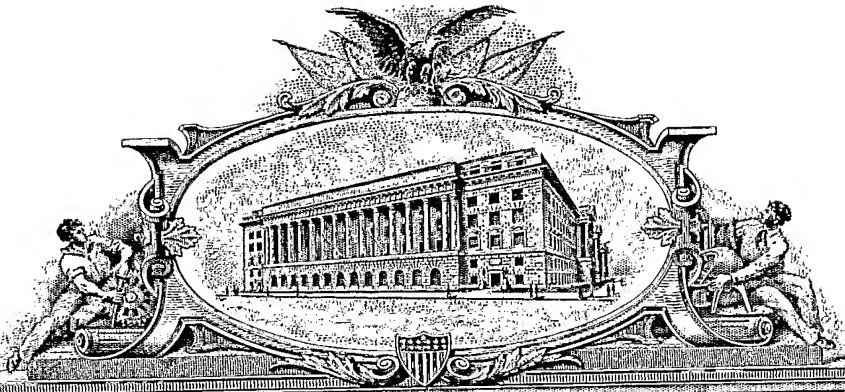
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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No.

INVENTOR(S)					
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Additional inventors are being named on the <u>1</u> separately numbered sheets attached hereto					
TITLE OF THE INVENTION (500 characters max)					
Ampipathic Molecules for Use in the Control of Drug Release					
Direct all correspondence to: CORRESPONDENCE ADDRESS					
<input type="checkbox"/> Customer Number: <div></div>					
OR					
<input checked="" type="checkbox"/> Firm or Individual Name		The University of British Columbia - Industry Liaison Office			
Address		#103 -6190 Agronomy Road			
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[Page 1 of 2]

Respectfully submitted,

SIGNATURE

Annari Faurie

TYPED or PRINTED NAME ANNARI FAURIE

TELEPHONE 604-822-8594

Date 20 February 2004

REGISTRATION NO.

(if appropriate)

Docket Number: UBC 02-118

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Docket Number UBC 02-118

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Number 1 of 1

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TO:

Commissioner for Patents
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Enclosures:

1. Provisional application for patent cover sheet
2. Specifications, 17 pages
3. Drawings, 2 pages
4. Credit card payment form PTO-2038 for \$80.00 filing fee

THE UNIVERSITY OF BRITISH COLUMBIA

February 20, 2004

Hon. Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Re: Provisional Patent Application for "Ampipathic Molecules for Use in the
Control of Drug Release"
UBC file no: 02-118

Enclosed please find the necessary documents for filing a Provisional Patent
Application for the above-identified technology on behalf of The University of British
Columbia. Also enclosed is Credit Card payment form PTO-2038 to cover the cost
of the \$80.00 application fee.

Thank you,

Sincerely,



Annari Faurie
Patent Manager

Encl.



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**AMPIPATHIC MOLECULES FOR USE IN THE CONTROL
OF DRUG RELEASE**

Inventors:

John Jackson, Helen Burt, Kevin Letchford

AMPIPATHIC MOLECULES FOR USE IN THE CONTROL OF DRUG RELEASE

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Abstract:

The present invention describes a method for controlling drug release from polymeric matrices. This may be achieved by the inclusion of amipathic molecules in a drug-loaded polymeric matrix so that the rate of dissolution of the amipathic molecules may affect the physical state of the polymeric matrix and either accelerate or inhibit drug release mechanisms. Control is exerted by matching the hydrophilic:hydrophobic ratio or the molecular weight of the components of the amipathic molecules to the release requirements of the drug from the polymeric matrix.

Field of Invention:

This invention relates to the field of improved drug delivery systems for use in the treatment of disease. The invention describes the use of the invention in the treatment of inflammatory, proliferative or angiogenic-related disease but the invention is not limited to treatment of these diseases. These diseases are discussed by way of illustration as being particularly suited to the methods described in this invention. However the invention may potentially be used to deliver any drugs to treat any disease in humans or animals.

BACKGROUND OF THE INVENTION

The present cost of treating proliferative, inflammatory or angiogenic-dependent diseases around the world is substantial. Often these diseases may persist in patients for weeks or months (chronic inflammation) requiring extended and costly care. Chronic inflammation may be described as that of a long duration in which active inflammation, tissue destruction and attempts at healing proceed simultaneously (see *Robbins Pathological Basis of Disease* by R.S. Cotran, V. Kumar and S.L. Robbins, W.B. Saunders Co., p75, 1989). Sometimes, inflammatory diseases will start as acute episodes (causing pain and economic loss to the patient) and develop into chronic inflammatory conditions with subsequent debilitating consequences to both the mental and physical well-being of the patient. Despite these severe consequences there are often few therapeutic options for patients with chronic inflammatory diseases such as arthritis, restenosis, psoriasis, multiple sclerosis, surgical adhesions, inflammatory bowel diseases and chronic inflammatory lung diseases. Often patients are treated temporarily with steroidal or non-steroidal anti-inflammatories to relieve the symptoms of the diseases but these therapies offer little long-term benefit and are associated with serious side effects if used too frequently (such as gastric ulcers from non-steroidal anti-inflammatories or more serious toxicities from steroidal abuse). The costs and problems associated with the treatment of cancer are huge and are discussed in detail in the background section of this invention.

Clearly, there exists in the medical profession a great need for compounds and effective methods of delivery that may treat these diseases more effectively. The complex and multifaceted nature of inflammatory diseases suggests that agents with singular molecular mechanisms of action may not be obvious candidates to achieve such therapeutic objectives. Interestingly, some compounds that were thought to have singular mechanisms of action are now being shown to display therapeutic potential against certain inflammatory diseases. For example the anti-folate, anticancer drug, methotrexate is now the most widely described drug for the aggressive treatment of rheumatoid arthritis yet the mechanism by which this drug works against this disease remains unknown (see Bannwarth B. et al. Review: Methotrexate in Arthritis in *Drugs* 47 (1) p25-50, 1994.) Similarly, Hunter et al. have described the effective use of the microtubule inhibitor and anti-cancer drug paclitaxel against a range of chronic inflammatory diseases (World patent PCT: WO 98/24427). Again, the exact mechanism of action of this drug in treating these

diseases is unknown since this drug not only stabilizes microtubules but it also inhibits central signalling factors involved in inflammatory diseases such as MAPkinase (Jackson J.K. et al in Immunology 1997, (90) p502-510) and AP1 (Hui A. et al Arthritis and rheumatism, 41(5) p 869-876 1998.).

It seems likely that in the future the pharmaceutical industry may be able to fully understand the pathophysiology of inflammatory diseases and customize combination therapies to treat all the molecular mechanisms that make up these inflammatory diseases. However, existing drugs may also offer immediate, but non-obvious therapeutic potential, as witnessed by the serendipitous discoveries of methotrexate and paclitaxel as disease modifying drug agents.

Often the use of powerful anti-proliferative or antiangiogenic drugs is limited by the toxicity of the drugs when they are delivered systemically by repeated dosing. Such administration methods are often characterized by peaks and troughs of drug concentrations in the blood so that excessive drug is administered to maintain drug efficacy in the therapeutic window for the drug. These methods may lead to undue toxicity to the whole body or specific organs and expose all tissues to these powerful drugs when only specific tissues may be the target. An improved method of delivering these drugs might be to use controlled release systems that maintain effective concentrations of the drugs at the disease site but minimize systemic toxicities associated with systemic delivery. Alternatively, controlled release systems may deliver the drugs to the systemic circulation but may optimally maintain the blood concentration within the therapeutic window but may avoid the peaks and troughs associated with normal administration methods such as oral tablets or i.v. injection.

The development of a new drug involves more than just the synthesis of a novel compound. Drugs must be transported to various locations within living systems by drug delivery systems; these systems perform controlled mechanisms that allow for the release of a drug so that it can reach the specified drug target. Controlled drug delivery occurs when a polymer is combined with a drug or any other active therapeutic agent in such a way that the drug is released from the material in a controlled fashion. The rate at which the drug is made available to the living system once it has been delivered, is dependant on the technology of the delivery system.

Present concerns with poor drug delivery involve too great an outflow or too little an outflow of the drug. When the outflow of the drug is too great, drug concentration increases and results in adverse side effects. On the other hand, when drug outflow is too low, the concentration of the drug may not provide the full therapeutic benefit. Therefore it is desirable to release drugs at a constant desired rate, thereby maintaining drug concentration within the therapeutic range and eliminating the need for frequent dosages.

Controlled drug release is achieved by the use of diffusion, chemical reactions, dissolutions or osmosis, used either singly or in combination. While the vast majority of such delivery devices are based on polymers, controlled release can also be achieved by the use of mechanical pumps.

Various situations arise when dealing with the molecular properties of certain therapeutic agents. For example, water-soluble drugs, low-solubility drugs, specific site drugs, two or more drugs are all factors that system based carriers must take into consideration. The ideal drug delivery system should be inert, biocompatible, mechanically strong, comfortable for the patient, capable of achieving high drug loading, safe from accidental release, simple to administer and remove, and easy to fabricate and sterilize. The need for such an innovative drug delivery system is evident within the medical field.

Controlled release of therapeutics has led to the development of numerous systems based on injection pumps, topical patches and implantable polymeric systems.

Often, the release of the drug(s) from such polymeric systems is controlled to the degree that the release of the drug occurs over a period of time but the release rate cannot be "tuned" to a required value other than by rather crude methods such as altering the loading of the drug in the polymer or altering the amount of polymer-drug implanted into the body. Clearly there exists a need for a method to exert a finer level of control of drug release from polymeric controlled release systems. This invention describes methods that exert such levels of control of drug release by the use of amphoteric molecules in the polymer-drug implant to affect the physical state of the polymer and to control the rate of drug release from the polymer. This

invention is suitable for use with a wide range of drugs directed at proliferative, inflammatory or angiogenic disorders such as those discussed in the following text.

Detailed Description of the Invention:

The use of polymeric materials to encapsulate drugs for controlled release *in vivo* is well known. The materials may take form of microspheres, pastes, films, and implants. The method for controlling drug release from such systems can be varied, but is largely dependent on the solubility of the drug in water. Methods of gaining better control may depend on drug loading, polymer degradation, system geometry or the inclusion of excipients that dissolve out of the polymer. The state of the drug in the polymer matrix may also affect drug release. For example, depending on drug loading, hydrophobic drugs often dissolve in hydrophobic polymeric matrices so that drug release may depend on the rate of diffusion of such drugs through the polymer matrix at the molecular level. Similarly, hydrophilic drug release from hydrophilic matrices may depend on the rate of drug diffusion.

Other workers have described the use of additives to polymeric implants to affect the rate of drug release from the implants. The patent EP 1013270A2 describes the inclusion of hydrophilic excipients in polymers to accelerate the release rate of water-soluble hormones. In the patent, these hydrophilic excipients such as salts and carbohydrates are incorporated into the polymer to increase water penetration and accelerate polymer erosion. Similarly, Badiger et al (Biomaterials 14 1993 p 1059-1063) described the addition of the highly water soluble additives based on polyethylene glycol derivatives to increase the rate of release of vitamin B12 from polymeric hydrogels. In another report Dordunoo et al (Journal of Controlled Release 44 1997 p 87-94) described the addition of water-soluble additives such as sodium chloride, albumin or gelatin to paclitaxel loaded polycaprolactone implants to accelerate drug release. Winternitz et al (Pharmaceutical Research 13 1996 p 368-375) showed that the addition of the water-soluble additive methoxypolyethylene glycol molecular weight 350 (MePEG) to paclitaxel loaded polycaprolactone implants actually inhibited drug release rates. Conversely Jackson et al (Br. J. Cancer 75 1997 p 1014-1020) showed that the addition of MePEG to a hydrophobic vanadium drug (BMOV) loaded polycaprolactone implant accelerated BMOV release. All these previous reports describe the ability to form a more porous polymeric implant *in vivo* by the addition of highly water-soluble additives to enable faster drug release. However, not only do the additives not always allow for accelerated drug release there is no level of control at which the additives dissolve out and form the porous structure. These water-soluble additives are not intended to form a miscible phase with the drug loaded hydrophobic polymeric implant. Rather they are suspended particulates or phase-separated blends where the additives are not fully associated with the hydrophobic polymer chains of the main matrix. The idea is that these additives need to dissolve out as soon as possible when placed in the body to accelerate drug release rates. Using these water-soluble additives, the only level of control of drug release rates may be achieved by the addition of different amounts of the excipients to increase the general porosity of the polymeric implant. These unsophisticated methods to increase release rates of drugs from implants do not control release rates to fit a desired dosing regime. The release profile may coincidentally fit the required regime but what is needed is a drug release system that allows much greater control of drug release rates.

This invention describes the use of specially synthesized amphipathic molecules to exert such control of drug release rates from polymers. A series of amphipathic block copolymers were synthesized from polycaprolactone (hydrophobic group) and MePEG (hydrophilic group) and were investigated for the utility of these copolymers to manufacture micellar compositions of hydrophobic drugs. Similar diblock copolymers (based on polylactic acid and MePEG) have been previously described as micellar carriers of the hydrophobic drug paclitaxel (Burt et al. Colloids and Surfaces B: Biointerfaces, 16 1996 p 161-171). However, it was noticed that these amphipathic copolymers did not form phase boundaries when blended with hydrophobic polymers such as ethylene vinyl acetate (EVA) and polylactic co-glycolic acid and were therefore miscible with the main polymer chains. It was also noticed that the rate at which these copolymers then dissolved out of the polymer was very slow, not fast like previously described highly water soluble additives such as MePEG.

This invention proposes that amphipathic molecules such as diblock copolymers may be blended into a polymer-drug composition to control drug release. It is proposed that diblock copolymers containing high ratios of hydrophilic to hydrophobic constituents will dissolve out of the polymer matrix quickly whereas copolymers manufactured from high ratios of hydrophobic to hydrophilic constituents will dissolve out

quite slowly. The release of such polymers may open up the main polymer matrix to water. In another embodiment of the invention, the controlled release of the ampipathic molecule may affect the rate of degradation of the main polymer matrix, which may in turn control drug release rates. By controlling the hydrophobic to hydrophilic ratio of the copolymer, the molecular weight of the copolymer and the degree of loading of the copolymers in the main polymer matrix, control of copolymer release and drug release may be improved. These methods affect the entry of water into the matrix.

However, in another embodiment of this invention, the release of such ampipathic molecules may also "open up" a polymer matrix so that the diffusion rates of drugs within the matrix are affected or controlled. This leads to the idea of establishing a molecular sieve *in vivo* after the polymer has been placed in the animal or human. For example, a cross linked polysaccharide (such as hyaluronic acid or chitosan) film may be used. Such films do not swell much in water, (Jackson et al Pharmaceutical Research 2002; (19): 4 p411-417) so that therapeutic agents, such as, for example the large molecular weight proteins or oligonucleotides may not move through the matrix quickly because the polymer chains may restrict the movement, effectively trapping the drugs in the film. If ampipathic molecules are included in such a matrix then the release of these molecules may allow for an enlargement of the effective pore size of the sieve, thus allowing for faster movement of the protein or oligonucleotide molecule.

This invention describes the concept of controlling drug release from polymeric matrices by initially controlling the rate dissolution of the blended ampipathic molecules from the matrix. This may subsequently control either the rate of water entry into a polymeric matrix, the rate of polymer degradation or may control the rate of drug diffusion through a polymer matrix .

The present invention describes the concept of controlling the degree of drug release from a polymeric matrix. This is achieved by regulating the ratio of hydrophilic to hydrophobic constituents in a copolymer that is mixed with a drug. The rate of drug diffusion through a polymer matrix by the inclusion of ampipathic molecules, in this case copolymers, can potentially improve present drug delivery systems.

Another advantage of the described system concerns the phenomena of a burst phase of drug release from implants during which the release is not well controlled and very fast. This is thought to arise from surface associated drug releasing quickly from the polymer. Often this is followed by a moderate phase of release and then a very slow release rate. These systems are controlled to some degree but not usually tunable to a require dosing regime. (See Winternitz et al (Pharmaceutical Research 13 1996 p 368-375).

In this invention , as the ampipathic molecules slowly dissolve out, the polymeric matrix may slowly become more porous and the drug deeper in the implant will be exposed to water. In other words as the drug available to be released closer to the surface decreases (burst phase and moderate phase of drug release), the inner regions of the implant with available drug become exposed to water. This system may allow for an extended moderate phase of drug release that better suits the required dosing regimes.

Another advantage of the described invention is the potential phenomena known as micellization. By this method the ampipathic molecules may reach a critical micelle concentration (cmc) in the aqueous environment inside the polymer or just outside the polymer. Such micellar environments may strongly increase the local concentration of the drug being released by acting as a sink for the drug leading to increased rates of drug dissolution.

Another advantage of the use of ampipathic molecules is that these molecules may also affect the permeability of cell membranes in the local environment and potentially increase drug penetration into target tissues. For example if a polymeric system described in this invention was placed inside a tumor then the ampipathic molecules might increase the uptake of anticancer drugs into the tumor cells. Alternatively, some drug may be trapped within micelles such as those described above. It is well known that micelles are often taken up into cells by various methods so that a certain level of drug transport into the cells may be facilitated by this method. Another advantage of such a system may be that the micelles may protect the drug from a degradative processes until they reach the target tissue. For example, if a polymeric drug release systems was implanted in the body intramuscularly to deliver low levels of a chemotherapy drug through the blood to the (e.g.) pancreas then the drug might be released trapped in

amphipathic molecular micelles but at a distant site the concentration of the amphipathic molecules might fall below the cmc so that the micelles destabilized and released all the drug at the required site in an active (non-degraded) form.

This invention is not limited to the use of diblock copolymers as the amphipathic molecules used to control drug release rates. Any suitably synthesized amphipathic molecule may be used for this purpose. The suitability of each molecule might be assessed by the ability to blend with other polymers and to dissolve from the polymer in a controlled manner. .

POLYMERIC FORMULATIONS

As noted above, although we understand that certain drugs may be administered by conventional routes of administration, preferred methods involve the use of drugs and a polymeric carrier. In addition to the wide array of drugs discussed above, compositions of the present invention are provided in a wide variety of polymeric carriers, including for example both biodegradable, non-biodegradable and water soluble compositions. Representative examples of biodegradable compositions include albumin, gelatin, starch, cellulose, dextrans, polysaccharides, fibrinogen, polyesters such as poly(D,L lactide), poly(D,L-lactide-co-glycolide), poly(E-caprolactone), poly(L-lactide) and copolymers of the aforementioned polymers, poly(glycolide), poly(hydroxybutyrate), poly(alkylcarbonate) and poly(orthoesters) (see generally, Illum, L., Davids, S.S. (eds.) "Polymers in controlled Drug Delivery" Wright, Bristol, 1987; Arshady, J. *Controlled Release* 17:1-22, 1991; Pitt, *Int. J. Phar.* 59:173-196, 1990; Holland et al., *J. Controlled Release* 4:155-0180, 1986). Representative examples of nondegradable polymers include EVA copolymers, ester, ether carbonate, urea based polyurethanes, silicone rubber, polytetrafluoroethylene, polycarbonates, nylon polymer, polyethylene terephthalate, polyethylene and poly(methylmethacrylate). Representative examples of water-soluble polymers include polyethylene glycol, polox, polyacrylic acid, poly vinyl pyrrolidone, many polysaccharides and polyvinyl alcohol. Particularly preferred polymeric carriers include polyethylene glycols, polyoxamers, polysaccharides, block copolymers of ethylene and propylene glycol such as poly(ethylene-vinyl acetate)(40% cross-linked), poly(D,L-lactic acid) oligomers and polymers, poly(L-lactic acid) oligomers and polymers, poly(glycolic acid), copolymers of lactic acid and glycolic acid, poly(caprolactone), poly(valerolactone), polyanhydrides, copolymers of poly(caprolactone) or poly(lactic acid) with polyethylene glycol, including all analogues, derivatives, conjugates and blends thereof.

Polymeric carriers may be fashioned in a variety of forms, including for example, microspheres, rod-shaped devices, pellets, capsules, films, pastes, gels, sprays, foams, and coatings or implantable medical devices (see, e.g., Goodell et al., *Am. J. Hosp. Pharm.* 43:1454-1461, 1986; Langer et al., "Controlled release of macromolecules from polymers", in *Biomedical polymers, Polymeric materials and pharmaceuticals for biomedical use*, Goldberg, E.P., Nakagim, A. (eds.) Academic Press, pp. 113-137, 1980; Rhine et al., *J. Pharm. Sci.* 69:265-270, 1980; Brown et al., *J. Pharm. Sci.* 72:1181-1185, 1983; and Bawa et al., *J. Controlled Release* 1:259-267, 1985). Drugs factors may be dissolved in the polymer, suspended as particles, linked by occlusion in the matrices of the polymer, bound by covalent linkages, or encapsulated in microcapsules. Within certain preferred embodiments of the invention, drug compositions are provided in non-capsular formulations such as microspheres (ranging from nanometers to micrometers in size), pastes, threads of various size, films and sprays.

Preferably, drug loaded compositions of the present invention (which comprise one or more drug, and a polymeric carrier) are fashioned in a manner appropriate to the intended use. Within certain aspects of the present invention, the drug loaded composition should be biocompatible, and release one or more drug factors over a period of several hours to months. For example, "quick release" or "burst" drug compositions are provided that release greater than 10%, 20%, or 25% (w/v) of an drug factor over a period of 7 to 10 days. Such "quick release" compositions should, within certain embodiments, be capable of releasing chemotherapeutic levels (where applicable) of a desired drug factor. Within other embodiments, "slow release" drug compositions are provided that release less than 1% (w/v) of a drug factor over a period of 7 to 10 days. Further, drug compositions of the present invention should preferably be stable for several months and capable of being produced and maintained under sterile conditions. Within certain aspects of the present invention, drug compositions may be fashioned in any size ranging from 50 nm to 500 μm , depending upon the particular use. For example, when used for some purposes (as discussed below), it is generally preferable to fashion the drug composition in microspheres of between 15 and 500 μm , preferably between 15 and 200 μm , and most preferably, between 25 and 150 μm . Alternatively, such compositions may also be readily applied as a "spray", which solidifies into a film or coating. Such sprays may be prepared from microspheres of a wide array of sizes, including for example, from 0.1 μm to 3 μm , from 10 μm to 30 μm , and from 30 μm to 100 μm .

Drug compositions may also be prepared, given the disclosure provided herein, for a variety of other applications. For example, for administration to the cornea, the drug factors of the present invention may be incorporated into, but not limited to, muco-adhesive polymers (e.g., polyacrylic acids such as

(CARBOPOL[®], dextran, hyaluronic acid, polymethacrylate, or starch (see LeYung and Robinson, *J. of Controlled Rel.* 5:223, 1988)), or nanometer-sized microspheres (see generally, Kreuter *J. Controlled Release* 16:169-176, 1991; Couvreur and Vauthier, *J. Controlled Release* 17:187-198, 1991).

Drug or compositions of the present invention may also be prepared in a variety of "paste" or gel forms. For example, within one embodiment of the invention, drug compositions are provided which are liquid at one temperature (e.g., temperature greater than 37°C, such as 40°C, 45°C, 50°C, 55°C or 60°C), and solid or semi-solid at another temperature (e.g., ambient body temperature, or any temperature lower than 37°C). Such "thermopastes" may be readily made given the disclosure provided herein.

Within another embodiment of the invention drug compositions are provided which are liquid at room temperature and form semi-solid implants at 37°C following injection. Within yet other aspects of the invention, the drug or compositions of the present invention may be formed as a film. Preferably, such films are generally less than 5, 4, 3, 2, or 1, mm thick, more preferably less than 0.75 mm or 0.5 mm thick, and most preferably less than 500 μm to 25 μm thick. Such films are preferably flexible with a good tensile strength (e.g., greater than 50, preferably greater than 100, and more preferably greater than 150 or 200 N/cm²), good adhesive properties (i.e., readily adheres to moist or wet surfaces), and has controlled permeability. Representative examples of such films are set forth below in the Examples.

POLYMERIC CARRIERS FOR THE RELEASE OF HYDROPHOBIC COMPOUNDS

Within further aspects of the present invention, polymeric carriers are provided which are adapted to contain and release a hydrophobic compound, the carrier containing the hydrophobic compound in combination with a carbohydrate, protein or polypeptide. Within certain embodiments, the polymeric carrier contains or comprises regions, pockets, or granules of one or more hydrophobic compounds. For example, within one embodiment of the invention, hydrophobic compounds may be incorporated within a matrix containing the hydrophobic compound, followed by incorporation of the matrix within the polymeric carrier. A variety of matrices can be utilized in this regard, including for example, carbohydrates and polysaccharides such as starch, cellulose, dextran, methylcellulose, and hyaluronic acid, proteins or polypeptides such as albumin, collagen and gelatin.

A wide variety of hydrophobic compounds may be released from the polymeric carriers described above, including for example: certain hydrophobic compounds which inhibit disease processes.

TREATMENT AND PREVENTION OF DISEASES

Drug compounds of the present invention, which are optionally incorporated within one of the carriers described herein to form a therapeutic composition, may be prepared and utilized to treat or prevent a wide variety of diseases. Representative examples of diseases that may be treated include, for example, Cancer, restenosis, vascular disease (such as aneurysms or restenosis), psoriasis, M.S., surgical adhesions, inflammatory bowel disease, inflammatory lung disease, angiogenic disorders, arterial embolization in arteriovenous malformations (vascular malformations), menorrhagia, acute bleeding, central nervous system disorders, and hypersplenism; inflammatory skin diseases such as psoriasis, eczematous disease (atopic dermatitis, contact dermatitis, eczema), immunobullous disease, pre-malignant epithelial tumors, basal cell carcinoma, squamous cell carcinoma, keratocanthoma, malignant melanoma and viral warts; ocular disease such as diabetic retinopathy and macular degeneration, inflammatory arthritis which includes a variety of conditions including, but not limited to, rheumatoid arthritis, mixed connective tissue disease, Sjögren's syndrome, ankylosing spondylitis, Behçet's syndrome, sarcoidosis, crystal induced arthritis and osteoarthritis (potentially) – all of which feature inflamed, painful joints as a prominent symptom.

Also, examples include stents and grafts, cardiovascular devices may be coated with or otherwise constructed to contain and/or release any of the drugs agents provided herein. Representative examples include cardiovascular devices (e.g., implantable venous catheters, venous ports, tunneled venous catheters, chronic infusion lines or ports, including hepatic artery infusion catheters, pacemaker wires, implantable defibrillators); neurologic/neurosurgical devices (e.g., ventricular peritoneal shunts, ventricular atrial shunts, nerve stimulator devices, dural patches and implants to prevent epidural fibrosis post-laminectomy, devices for continuous subarachnoid infusions); gastrointestinal devices (e.g., chronic indwelling catheters, feeding tubes, portosystemic shunts, shunts for ascites, peritoneal implants for drug delivery, peritoneal dialysis catheters, implantable meshes for hernias, suspensions or solid implants to prevent surgical adhesions, including meshes); genitourinary devices (e.g., uterine implants, including intrauterine devices (IUDs) and devices to prevent endometrial hyperplasia, fallopian tubal implants, including reversible sterilization devices, fallopian tubal stents, artificial sphincters and periurethral implants for incontinence, ureteric stents, chronic indwelling catheters, bladder augmentations, or wraps or splints for vasovasostomy); ophthalmologic implants (e.g., multino implants and other implants for neovascular glaucoma, drug eluting contact lenses for pterygiums, splints for failed dacrocystorhinostomy, drug eluting contact lenses for corneal neovascularity, implants for diabetic retinopathy, drug eluting contact lenses for high risk corneal transplants); otolaryngology devices (e.g., ossicular implants, Eustachian tube splints or stents for glue ear or chronic otitis as an alternative to transtympanic drains); plastic surgery implants (e.g., prevention of fibrous contracture in response to gel- or saline-containing breast implants in the subpectoral or subglandular approaches or post-mastectomy, or chin implants), and orthopedic implants (e.g., cemented orthopedic prostheses).

Complications Associated with Access Devices

Venous access devices, such as external tunneled catheters (e.g., Hickman®/Broviac® and Groshong®) and implanted ports, are commonly used for prolonged venous access in many disease processes. Other access devices include epidural catheters and peripherally inserted central catheters (PICCs). The most common complications associated with these devices are infection and thrombosis. Others include extravasation, catheter damage and catheter dislodgement (Dearborn *et al.*, 1997).

Infection is a complication of all types of access devices (Ascher *et al.*, 1993; Decker & Edwards, 1988; Early *et al.*, 1990; Lam *et al.*, 1994; Press *et al.*, 1984; Raad *et al.*, 1993), including epidural catheters (Williams *et al.*, 1990). Local infections, including exit-site, port pocket and tunnel infections can occur, as well as systemic infections from colonized thrombi or fibrin sleeves or from intraluminal or extraluminal catheter colonization, with incidence ranging from 2% to 44% (reviewed in Dearborn *et al.*, 1997; Wickham *et al.*, 1992). If this complication persists following appropriate antibiotic treatment, current recommendations are to remove the device (Decker & Edwards, 1988). Some organisms are particularly hard to eliminate because they preferentially bind to catheter surfaces and are capable of producing a slime-like glycocalyx that may resist antibiotics and host defense mechanisms.

Greater numbers of infections occur with multilumen catheters compared with single lumen catheters (Dearborn *et al.*, 1997; Early *et al.*, 1990; McCarthy *et al.*, 1987). Although some investigators report lower infection rates with implanted ports than with external tunneled devices, others have demonstrated no difference in incidence of infections (Carde *et al.*, 1989; Dearborn *et al.*, 1997; Wurzel *et al.*, 1988). Dearborn *et al.* (1997) found that a greater infection rate was associated with Groshong® catheters when compared to Hickman® catheters and implanted ports.

Extraluminal obstruction from mural thrombus, fibrin sleeve or clot formation at the catheter tip is frequently associated with catheter-related infections (Rupar *et al.*, 1990; Schuman *et al.*, 1985). Press *et al.* (1984) demonstrated that catheter thrombosis was the primary prognostic factor for infections in tunneled catheters.

It is also envisaged that some of these drug agents will have antibacterial effects so that drug released from such implants will also inhibit bacterial growth.

In the case of stents, a wide variety of stents may be developed to contain and/or release the drug agents provided herein, including esophageal stents, gastrointestinal stents, vascular stents, biliary stents, colonic stents, pancreatic stents, ureteric and urethral stents, lacrimal stents, Eustachian tube stents, fallopian tube stents, nasal stents, sinus stents and tracheal/bronchial stents. Stents may be readily obtained from commercial sources, or constructed in accordance with well-known techniques. Representative examples of stents include those described in U.S. Patent No. 4,768,523, entitled "Hydrogel Adhesive"; U.S. Patent No. 4,776,337, entitled "Expandable Intraluminal Graft, and Method and Apparatus for Implanting and Expandable Intraluminal Graft"; U.S. Patent No. 5,041,126 entitled "Endovascular Stent and Delivery System"; U.S. Patent No. 5,052,998 entitled "Indwelling Stent and Method of Use"; U.S. Patent No. 5,064,435 entitled "Self-Expanding Prosthesis Having Stable Axial Length"; U.S. Patent No. 5,089,606, entitled "Water-insoluble Polysaccharide Hydrogel Foam for Medical Applications"; U.S. Patent No. 5,147,370, entitled "Nitinol Stent for Hollow Body Conduits"; U.S. Patent No. 5,176,626, entitled "Indwelling Stent"; U.S. Patent No. 5,213,580, entitled "Biodegradable Polymeric Endoluminal Sealing Process"; and U.S. Patent No. 5,328,471, entitled "Method and Apparatus for Treatment of Focal Disease in Hollow Tubular Organs and Other Tissue Lumens."

Other representative diseases include inflammatory bowel disease (IBD) which is the general term for a group of chronic inflammatory disorders of unknown etiology involving the gastrointestinal tract - chronic IBD is divided into 2 groups: ulcerative colitis and Crohn's disease; surgical adhesions; periodontal disease; polycystic kidney disease, chronic inflammatory diseases of the respiratory tract including asthma, chronic obstructive pulmonary disease (COPD) which includes a variety of conditions (chronic bronchitis, asthmatic bronchitis, chronic obstructive bronchitis and emphysema) which lead to chronic airway obstruction; a wide variety of diseases associated with the obstruction of body passageways, including for example, vascular diseases, neoplastic obstructions, inflammatory diseases, and infectious diseases; and also neovascular diseases of the eye including for example, corneal neovascularization, neovascular glaucoma, proliferative diabetic retinopathy, retrolental fibroplasia and macular degeneration.

For example, within one aspect of the present invention certain drug agents and compositions as described herein may be utilized to treat vascular diseases that cause obstruction of the vascular system. Representative examples of such diseases include arteriosclerosis of all vessels (around any artery, vein or graft) including, but not restricted to: the coronary arteries, aorta, iliac arteries, carotid arteries, common femoral arteries, superficial femoral arteries, popliteal arteries, and at the site of graft anastomosis; vasospasms (e.g., coronary vasospasms and Raynaud's disease); restenosis (obstruction of a vessel at the site of a previous intervention such as balloon angioplasty, bypass surgery, stent insertion and graft insertion); inflammatory and autoimmune conditions (e.g., temporal arteritis, vasculitis).

Within other aspects of the invention, the drug therapeutic agents or compositions described herein may be utilized to treat neoplastic obstructions. Briefly, as utilized herein, a "neoplastic obstruction" should be understood to include any neoplastic (benign or malignant) obstruction of a bodily tube regardless of tube location or histological type of malignancy present. Representative examples include gastrointestinal diseases (e.g., oral-pharyngeal carcinoma adenocarcinoma, esophageal carcinoma (squamous cell, adenocarcinoma, lymphoma, melanoma), gastric carcinoma (adenocarcinoma, linitis plastica, lymphoma, leiomyosarcoma), small bowel tumors (adenomas, leiomyomas, lipomas, adenocarcinomas, lymphomas, carcinoid tumors), colon cancer (adenocarcinoma) and anorectal cancer);

biliary tract diseases (e.g., neoplasms resulting in biliary obstruction such as pancreatic carcinoma (ductal adenocarcinoma, islet cell tumors, cystadenocarcinoma), cholangiocarcinoma and hepatocellular carcinoma); pulmonary diseases (e.g., carcinoma of the lung and/or tracheal/bronchial passageways (small cell lung cancer, non-small cell lung cancer)); female reproductive diseases (e.g., malignancies of the fallopian tubes, uterine cancer, cervical cancer, vaginal cancer); male reproductive diseases (e.g., testicular cancer, cancer of the epididymus, tumors of the vas deferens, prostatic cancer, benign prostatic hypertrophy); and urinary tract diseases (e.g., renal cell carcinoma, tumors of the renal pelvis, tumors of the urinary collection system such as transitional cell carcinoma, bladder carcinoma, and urethral obstructions due to benign strictures, or malignancy).

Within other aspects of the invention, the drug therapeutic agents and compositions may be utilized for preventing or treating inflammatory diseases which affect or cause the obstruction of a body passageway. Inflammatory diseases include both acute and chronic inflammation which result in obstruction of a variety of body tubes. Representative examples include vasculitis (e.g., Giant cell arteritis (temporal arteritis, Takayasu's arteritis), polyarteritis nodosa, allergic angiitis and granulomatosis (Churg-Strauss disease), polyangiitis overlap syndrome, hypersensitivity vasculitis (Henoch-Schonlein purpura), serum sickness, drug-induced vasculitis, infectious vasculitis, neoplastic vasculitis, vasculitis associated with connective tissue disorders, vasculitis associated with congenital deficiencies of the complement system), Wegener's granulomatosis, Kawasaki's disease, vasculitis of the central nervous system, Buerger's disease and systemic sclerosis); gastrointestinal tract diseases (e.g., pancreatitis, Crohn's disease, ulcerative colitis, ulcerative proctitis, primary sclerosing cholangitis, benign strictures of any cause including idiopathic (e.g., strictures of bile ducts, esophagus, duodenum, small bowel or colon)); respiratory tract diseases (e.g., asthma, hypersensitivity pneumonitis, asbestosis, silicosis, and other forms of pneumoconiosis, chronic bronchitis and chronic obstructive airway disease); nasolacrimal duct diseases (e.g., strictures of all causes including idiopathic); and eustachean tube diseases (e.g., strictures of all causes including idiopathic).

Within yet other aspects of the present invention, the drug, therapeutic agents and compositions may be utilized for treating or preventing infectious diseases that are associated with, or causative of, the obstruction of a body passageway. Briefly, infectious diseases include several acute and chronic infectious processes can result in obstruction of body passageways including for example, obstructions of the male reproductive tract (e.g., strictures due to urethritis, epididymitis, prostatitis); obstructions of the female reproductive tract (e.g., vaginitis, cervicitis, pelvic inflammatory disease (e.g., tuberculosis, gonococcus, chlamydia, enterococcus and syphilis)); urinary tract obstructions (e.g., cystitis, urethritis); respiratory tract obstructions (e.g., chronic bronchitis, tuberculosis, other mycobacterial infections (MAI, etc.), anaerobic infections, fungal infections and parasitic infections); and cardiovascular obstructions (e.g., mycotic aneurysms and infective endocarditis).

Applications of the invention: the following uses are given as examples only and are not intended to restrict the application of the invention.

Restenosis: Stents might be coated with a polymer such as EVA blended with a diblock copolymer (such as those described in this invention) containing a drug such as paclitaxel.

Perivascular treatment of restenosis: A film made from EVA blended with a diblock copolymer (such as those described in this invention) containing a drug such as paclitaxel might be wrapped around a blood vessel.

Perivascular treatment of restenosis: A paste made from a polymer blended with a diblock copolymer (such as those described in this invention) containing a drug such as paclitaxel might be injected around a blood vessel.

Arthritis: Microspheres made from poly lactic acid blended with a diblock copolymer (such as those described in this invention) containing a drug such as paclitaxel might be injected into the joint

Systemic drug delivery : A paste made from a polymer blended with a diblock copolymer (such as those described in this invention) containing a drug such as paclitaxel might be injected intramuscularly.

Micellar Systemic or local drug delivery: A paste made from a polymer blended with a diblock copolymer (such as those described in this invention) containing a drug such as paclitaxel might be injected intraperitoneally whereby the released diblock might micellize the drug paclitaxel.

Psoriasis: A topical cream/paste/gel made from a polymer blended with a diblock copolymer (such as those described in this invention) containing a drug such as paclitaxel might be applied to the skin. A patch containing the formulation might similarly applied.

Oral formulation: A paste made from a polymer blended with a diblock copolymer (such as those described in this invention) containing a drug such as paclitaxel might be given orally. This might be for GI uptake into the systemic circulation or to treat disorders of the GI tract such as IBD or cancer.

Surgical adhesions: A film made from a copolymer such as caprolactone-co-dextran containing a diblock copolymer (such as those described in this invention) containing a drug such as paclitaxel might be applied to the surgical site.

Systemic drug delivery: A paste or microsphere preparation made from polylactic coglycolic acid implants containing a diblock copolymer (such as those described in this invention) containing a drug such as a hormone, protein , nucleic acid (eg oligonucleotide or ribozyme) or small molecule drug might be implanted in the body.

A paste or microsphere preparation made from crosslinked hyaluronic acid films containing a drug such as a hormone, protein , nucleic acid (eg oligonucleotide or ribozyme) or small molecule drug might be implanted in the body.

Formulation and Administration

As noted above, therapeutic compounds may be formulated in a variety of forms (e.g., microspheres, pastes, films, sprays, ointments, creams, gels and the like). Further, the compositions of the present invention may be formulated to contain more than one drug agent, to contain a variety of additional compounds, to have certain physical properties (e.g., elasticity, a particular melting point, or a specified release rate). Within certain embodiments of the invention, compositions may be combined in order to achieve a desired effect (e.g., several preparations of microspheres may be combined in order to achieve both a quick and a slow or prolonged release of one or more drug agents).

Polymeric formulations of drug agents may be administered either alone, or in combination with pharmaceutically or physiologically acceptable carrier, excipients or diluents. Generally, such carriers should be nontoxic to recipients at the dosages and concentrations employed. Ordinarily, the preparation of such compositions entails combining the polymeric formulation of the therapeutic agent with buffers, antioxidants such as ascorbic acid, low molecular weight (less than about 10 residues) polypeptides, proteins, amino acids, carbohydrates including glucose, sucrose or dextrans, chelating agents such as EDTA, glutathione and other stabilizers and excipients. Neutral buffered saline or saline mixed with nonspecific serum albumin are exemplary appropriate diluents.

As noted above, drug agents, compositions, or pharmaceutical compositions provided herein may be prepared for administration by a variety of different routes, including for example, orally, nasally, topically to a site of inflammation, rectally, intracranially, intrathecally, intranasally, intraocularly, intraarticularly, subcutaneously, intraperitoneally, intramuscularly, sublingually and intravesically. Other representative routes of administration include direct administration (preferably with ultrasound, CT, fluoroscopic, MRI or endoscopic guidance) to the disease site.

The therapeutic agents, therapeutic compositions and pharmaceutical compositions provided herein may be placed within containers, along with packaging material which provides instructions regarding the use of such materials. Generally, such instructions include a tangible expression describing the reagent concentration, as well as within certain embodiments, relative amounts of excipient ingredients or diluents (e.g., water, saline or PBS) which may be necessary to reconstitute the drug agent, or pharmaceutical composition.

Examples:

The following examples are meant to help illustrate, but not limit, the present invention.

EXAMPLE 1

Polymer synthesis and Characterization

A series of MePEG-b-PCL diblock copolymers with varying MePEG and PCL block lengths was synthesized using a ring opening polymerization using stannous octoate as a catalyst. MePEG with molecular weights of 550, 750 or 2000 were combined with ϵ -caprolactone in varying weight ratios to control the final molecular weight of the copolymer. The reagents were placed in a round bottom flask sealed with a ground glass stopper and immersed in a heavy mineral oil bath heated to 140°C. The mixture was stirred with a teflon coated magnetic stir bar. After mixing for 30 minutes 0.15ml of stannous octoate was added to the flask. The reaction was allowed to proceed for 12 hours. 300MHz proton NMR spectra of a 10% w/v solution of copolymer in deuterated chloroform was used to determine the degree of polymerization of the final products (figure 1). Copolymer molecular weight and polydispersity index was measured by gel permeation chromatography (GPC) against PEG standards in the range of 670 to 118400 g/mol. Chloroform was used as a mobile phase and separation was achieved through two Styragel columns (HR 0.5 and HR3). Detection was by a refractive index detector.

Micelle Characterization

The critical micelle concentration (CMC) was determined by the use of the fluorescence probe pyrene. When pyrene partitions into the hydrophobic domain of a polymeric micelle changes occur in the excitation spectra of pyrene. The (0,0) band shifts from a maximum at 333nm to 336nm. The ratio of the excitation intensity at 336nm vs. that at 333nm (I_{336}/I_{333}) was used to determine the CMC. Aqueous solutions of diblock copolymer at varying concentrations were added to vials containing pyrene at a final concentration of 6×10^{-7} M. The solutions were allowed to equilibrate with stirring in the dark at 37°C for 24hrs. At the time of measurement, using a spectrofluorometer, the samples were excited at wavelengths ranging from 300 to 350 nm and the emission wavelength set at 390nm. Plots of I_{336}/I_{333} vs. log copolymer concentration were prepared (figure 2). The CMC was determined from the intersection of two straight lines (the horizontal line with an almost constant value of I_{336}/I_{333} and the diagonal line with a steady increase in the ratio value). Average size and size distribution of micelles in phosphate buffered saline at concentrations well above the CMC at a temperature of 37°C was measured using a Malvern Zetasizer with a wavelength of 633nm. The intensity of scattered light was detected at 90° to the incidence beam.

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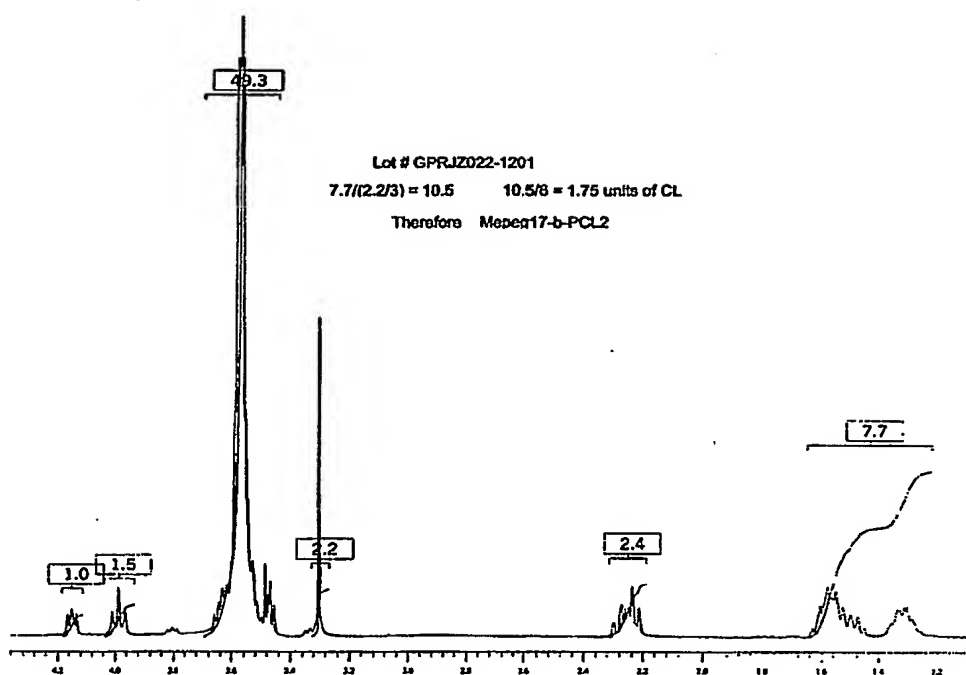


Figure 1: NMR spectra of MePEG-b-PCL

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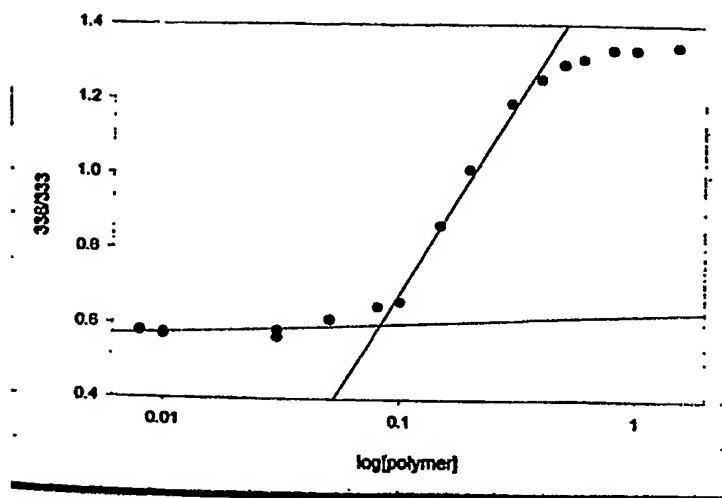


Figure 2: plot of I_{336}/I_{333} vs. \log copolymer concentration for CMC determination

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